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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,484	03/25/2002	Jacques Alexandre Hatzfeld	USB 99 AH CNR SOMA	5595

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,484	HATZFELD ET AL.	
	Examin r	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1,8,9,11 and 21-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,9,11 and 21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/22/06 has been entered.

Applicants' Remarks and Amendments to the claims have been entered. Claims 1, 8, 9, 11 are amended; claims 1, 8, 9, 11, 21-26 are pending and under current examination.

Claim Objections

Claim 21 is objected to because of the following informalities:

1) line 3 of the claim recites "hum" stem cells. It appears that this is a typographical error, and is intended to recite "human" stem cells.

2) Line 10 of the claim recites "activin", this appears to be a misspelling of "antivin".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The prior rejection of claims 1-16, 18-20 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants' amendment to the claims, which no longer recite "embryonic stem cells at the origin of somatic stem cells, " stem cells at the origin of blood, and various other tissues".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

Methods of maintaining a non-differentiated state of human hematopoietic stem cells, while allowing cell division of said cells, the method comprising administering to said stem cells, TGFβ in the amount of 0.01 pg/ml to 1 mg/ml, in sequential combination with an anti-TGFβ in the amount of 0.1 μg/ml to 10mg/ml, wherein the stem cells are present in a cell concentration of about 1 to about 10^{10} cells per ml.

The specification does not reasonably provide enablement for the breadth of the claims, which encompass using antivin; and using stem cells other than hematopoietic stem cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments. Applicants believe that the claims are now enabled because they recite homogenous populations of cells, inhibitor and anti-inhibitors that are taught or exemplified in the present specification. See page 8 of the Response.

Response to Arguments. Applicants' amendments and arguments have been fully considered, but are not persuasive. The term "anti-TGFβ" is found to be enabled by the claims, because the specification contemplates this as anti-TGFβ

antisense oligonucleotides or blocking antibodies, which Fortunel *et al.* (**J. of Cell Science**, 111: 1867-1875 (1998)) teach as being equally effective in neutralizing the biological activity of TGFβ (see page 1868, 1st ¶, last sentence). However, the claims are not enabled for their breadth, because they encompass using inhibitors such as TGFβ or antivin, and utilizing the methods with either hematopoietic stem cells (HSCs) or embryonic stem (ES) cells. As stated in the Office action, mailed 1/25/05, pages 9-10, the state of the art of culturing stem cells in an undifferentiated state, but allowing them to divide, is found to be unpredictable. ES cells require different factors to maintain them in an undifferentiated state. Furthermore, although the specification and the art support using TGFβ/anti-TGFβ for HSCs, one could not readily apply these methods for ES cells. The specification provides no working examples, guidance or nexus for using the claimed methods for ES cells. Furthermore, the newly added claims recite using TGFβ or antivin as the inhibitor. The specification fails to provide guidance with regard to utilizing antivin as an inhibitor for either HSCs or ES cells. Applicants have provided Thisse *et al.* as support that antivin is a TGFβ family member. However, Thisse *et al.* is not within the scope of the instant invention, as their studies are directed to *in vivo* induction of the zebrafish antivin in development of zebrafish embryos. Thisse *et al.* show that overexpression of antivin abolishes mesoderm induction. However, they are not within the scope of the claims, which is *in vitro* assay using human stem cells.

Thus, when taken with the lack of any particular and specific guidance provided by the specification for with regard to using antivin in the claimed methods, as an inhibitor of cell development, and the lack of guidance or teachings provided by the specification with regard to utilizing the claimed methods with ES cells, as well as the state of the art, which finds maintaining cells in an undifferentiated state to be unpredictable, the lack of nexus between the claimed using the claimed methods with HSCs versus ES cells, it would have required

undue and unpredictable experimentation for one of skill in the art to practice the claimed invention.

New Matter

Claims 21-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Claim 21, as instantly amended, introduces new matter into the disclosure. Particularly, the addition of claims to include antivin as an inhibitor is not found to be supported by the originally-filed disclosure. MPEP § 2163.02 teaches that, "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. Although Applicants have provided Thisse *et al.* as support for antivin to be a member of the TBF-β family, the specification, as originally filed, does not contemplate or support antivin as an inhibitor of cell development of hematopoietic stem cells, or embryonic stem cells, which is what required by the claims. The lack of support in the specification for utilizing antivin, in the claimed methods, has been determined as new matter.

MPEP § 2163.06 notes, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP § 2163.06 further notes, "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure."

To the extent that the methods are not described in the instant disclosure, claims 21-26 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 11, 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9, as written, is unclear. The claim, which is dependent upon claim 1, recites that the inhibitor of cell development is synthesized by the stem cells. However, claim 1 recites that the stem cells are administered the inhibitor. Thus, it is unclear how claim 9's recitation of synthesis by the stem cells, relates to claim 1's step of administration. Claim 23 is similarly unclear, as it recites the same limitations as stated above. Appropriate correction is required.

Claim 11 recites the limitation "the multiplication process" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The prior rejection of claims 1-16 and newly added claim 19 under 35 U.S.C. 102(b) as being anticipated by Xi *et al.* is withdrawn because they do not teach using TGFβ as an inhibitor, and anti-TGFβ as an inhibitor for maintaining CD34+ stem cells, as now required by the claims.

The prior rejection of claims 1, 2, 4, 5-9, 12, 14, and newly added claim 19, under 35 U.S.C. 102(e) as being anticipated by Moore *et al.* is withdrawn because they do not teach using TGFβ as an inhibitor, and anti-TGFβ as an inhibitor for maintaining CD34+ stem cells, as now required by the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35

U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 8, 9, 11, 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzfeld *et al.* (cited previously) when taken with Fortunel *et al.* (**J. of Cell Science**, 111: 1867-1875 (1998)).

Hatzfeld teach that endogenous or added TGF-β down-modulates various cytokine receptors, and that this effect can be suppressed within 6 hours by the addition of anti-TGF-β antibodies, or antisense nucleotides. Hatzfeld study the release from TGF-β growth inhibition of high proliferative potential-quiescent primitive progenitors to understand whether this inhibitor is a central regulator of the stem cell compartment. They teach that these observations are used in developing an *in vitro* assay which combines receptor induction by anti-TGF-β together with optimal cytokine stimulation which can be performed using non purified hematopoietic progenitors. They teach that this method can render quiescent primitive progenitors responsive to optimal combinations of cytokines to improve the *in vitro* expansion of clinical samples. They teach the neutralization of an inhibitor of cell development (i.e., TGF-β). They further teach using these methods on CD34+ cells.

Hatzfeld *et al.* differ from the claimed invention, in that they do not teach specific amounts of added TGF-β or specific amounts of anti-TGFβ. However, prior to the time of the claimed invention, Fortunel *et al.* teach culturing CD34+ stem cells with 2 or 5 ng/ml of TGFβ and 5μg/ml of anti-TGFβ blocking antibody (see page 1868, col. 1-2, Hematopoietic growth factors and antibody). They teach that anti-TGF β releases the cells from quiescence, thus allowing them to divide (see Abstract). They teach amounts of TGFβ, which are within the range required by claims 1, 11, 21 (0.01 pg/ml to 1 mg/ml, 10^{-10} mg/ml to 1 mg/ml, and 0.01 pg/ml to 1 mg/ml, respectively). They teach culturing cells, which falls within the claimed range of 1 to about 10^{10} cells per ml, as required by claims 8 and 22.

Thus, given the combined teachings of Hatzfeld *et al.* and Fortunel *et al.*, it would be obvious for one of skill in the art to use the specific ranges, as taught by Fortunel *et al.*, to the assay, as taught by Hatzfeld *et al.*, with a reasonable expectation of success. One of ordinary skill would have been motivated use the specific ranges, as taught by Fortunel they show that the anti-TGFβ blocking antibody effectively neutralizes exogenously added TGFβ, (p. 1868, 2nd col., 1st ¶), and they suggest using TGFβ/ anti-TGFβ in an assay detect quiescient progenitor cells (HPP-Q cells) (p. 1870-71, bridging ¶), the same assay suggested by Hatzfeld *et al.*.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

thaian ton

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